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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,010	05/05/2005	Theodore L. DeWeese	59564(71699)	2794

7590 01/08/2008

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1635	

MAIL DATE	DELIVERY MODE
01/08/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,010	DEWEESE ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,23-25,50 and 51* is/are pending in the application.

4a) Of the above claim(s) *50 and 51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 23-25* is/are rejected.

7)☒ Claim(s) *3, 25* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 May 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of group I claims 1-3 and 23-25 in the reply filed 09/05/2007 is acknowledged.

Status of the Application

Claims 1-3, 23-25 and 50-51 are pending. Claims 1-3 and 23-25 are currently under examination. Claims 50-51 are withdrawn as being drawn to a non-elected invention.

Claim Objections

Claims 3 and 25 are objected to as reciting non-elected subject matter. Claims 3 and 25 should be rewritten deleting any non-elected subject matter.

Drawings

The drawings filed on 05/05/2005 are objected to under 37 CFR 1.83(a) because they fail to show the specific details as disclosed in the brief description on pages 4-7 of the specification. For instance, Figures 1-4 are said to depict Western blot analysis and transfection efficiencies represent in graph however the drawings are blurred and the specific lanes in the blot or the labeled columns in the graph are indiscernible. Further, Figure 25 depicts siRNA sequences with highlighted regions however the regions are shown as dark boxes and the specific sequence inside the highlighted region is not shown. Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). Corrected drawing

sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of killing a tumor cell in vitro comprising

contacting the cell in vitro with a small inhibitory RNA specific for a DNA repair protein and at least one DNA-damaging agent, does not reasonably provide enablement for a method of killing a tumor cell comprising contacting the cell in vivo with a siRNA specific for a DNA repair protein and at least one DNA-damaging agent.

Furthermore, claims 23-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The following factors have been considered in the analysis of enablement: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Claims 1-3 are drawn to a method of killing a tumor cell comprising contacting the cell with at least one siRNA specific for a DNA repair protein and at least one DNA damaging agent. The scope of claims 1-3 encompasses contacting tumor cells in vivo. Claims 23-25 are drawn to a method of treating a subject having cancer comprising administering to the subject a therapeutically effective amount of at least one siRNA specific for a DNA repair protein and a therapeutically effective amount of at least one DNA-damaging agent.

The nature of the invention relies upon contacting a tumor cell in vivo with a siRNA and inhibiting expression of a DNA repair protein such that the tumor cell is killed and a method of treatment of cancer occurs.

Whether the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art. The state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed. See MPEP § 2164.05(b). The state of the prior art provides evidence for the degree of predictability in the art and is related to the amount of direction or guidance needed in the specification as filed to meet the enablement requirement. The state of the prior art is also related to the need for working examples in the specification.

The state of the art for a given technology is not static in time. It is entirely possible that a disclosure filed on January 2, 1990, would not have been enabled. However, if the same disclosure had been filed on January 2, 1996, it might have enabled the claims. Therefore, the state of the prior art must be evaluated for each application based on its filing date. 35 U.S.C. 112 requires the specification to be enabling only to a person "skilled in the art to which it pertains, or with which it is most nearly connected." The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. >

Chiron Corp. v.Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1325-26 (Fed. Cir.2004).

A thorough review of the patent and non-patent literature indicates that the state of the art for in vivo applications using siRNA was unpredictable as observed by Caplen (Expert Opin. Biol. Ther. 2003, 3(4): 575-586) who states "[m]any of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system, have been problems the gene therapy field has struggled with for over a decade now" (see page 581, last paragraph). Novina et al. (Nature 2004, Vol.430:161-164) agrees that the "major obstacle to therapeutic gene silencing is the 'delivery problem'- the necessity of introducing short dsRNAs into specific organs" (see page 164, third paragraph).

Paroo et al. (Trends in Biotechnology 2004, Vol.22(8):390-394) summarizes by stating "[d]eveloping siRNA for efficient gene silencing in vivo is likely to be more challenging and many issues must be addressed before use in animals can become routine. As with any compound, issues of adsorption, distribution, metabolism and excretion are significant obstacles. However, the duplex nature of siRNA introduced an additional layer of complexity. Even with the great progress that has been made, it is not clear whether or not siRNA possesses any advantages relative to traditional antisense oligonucleotides for in vivo experiments or therapeutic development. Crucial

pharmacological and chemical challenges will need to be addressed before siRNA can fulfill its immense promise" (see page 393, last paragraph).

Although RNAi has been seen as the new magic bullet to silence genes, "...magic bullets need magic guns" (stated by William Pardridge as quoted by Adams in The Scientist (2005) Vol.19:Issue1). Adams notes that researchers have struggled to get their therapies to particular targets and as stated by McCaffrey "[t]heir approach involves injecting large amounts of virus [vectors expressing shRNA] into the tail vein of mice, or into an artery leading to the liver. Its efficient but probably isn't going to work for humans" (see page 2 The Scientist (2005) Vol.19:Issue1). Even some of the applicants of the instant application have noted the unpredictability of using siRNA injected into the vein and observes that "[i]n some cells, inhibition seemed nearly complete, whereas in others, low or moderate levels of EGFP were observed....These results may be due to incomplete inhibition in cells that take up lesser amounts of siRNA. High pressure delivery of fluorescently labeled siRNA reveals that in vivo uptake is not equal in all hepatocytes when this method is used' (Lewis et al. Nature Genetics 2002 Vol.32;107-108).

The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention,

and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. >See, e.g., Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004).

While the level of one of ordinary skill practicing said invention would be high, the level of predictability is considered variable as evident in the prior art discussed above and is not considered to provide sufficient enablement to practice the claimed invention. At best, the prior art at the time of the instant invention invites further experimentation to find a method of efficiently delivering siRNA to a cell or organism in vivo such that stability of the siRNA is achieved in vivo, the siRNA targets the specific cell or tissue, the siRNA dosage and toxicity is determined, sufficient entry of the siRNA into the cell in vivo and the effective action therein, namely inhibition of expression of any DNA repair protein such that the tumor cells are killed thereby effectuating a treatment for cancer.

The specification does not disclose a working embodiment of the instantly claimed invention of delivering a siRNA targeted to a DNA repair protein in vivo such that any cancer cell is killed. While the MPEP § 2164.02 states the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. In re Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970), the lack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art.

Thus, as discussed above, that there is a high level of unpredictability in the siRNA art for therapeutic in vivo applications. Furthermore, given there is no guidance in the specification that would be considered enabling for the breadth of the claimed subject matter and there is no working embodiment of in vivo delivery of siRNA targeted to a DNA repair protein such that siRNA is shown to enter the cell, target the DNA repair protein and decrease expression of said protein. The scope of the claims in view of the specification as filed together do not reconcile the unpredictability in the art to enable one of skill in the art to make and/or use the claimed invention. Without further guidance, one of skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Collis et al. (Nucleic Acids Research 2001, Vol. 29, No. 7: 1534-1538).

Claim 1 is drawn to a method of killing a tumor cell comprising contacting the cell with at least one small inhibitory RNA (siRNA) specific for a DNA repair protein and at least one DNA damaging agent. The instant specification does not define a siRNA

structurally and discloses a small inhibitory RNA as being specific for a DNA repair protein and capable of decreasing expression of said DNA repair protein therefore for prior art purposes the claims must be given their broadest reasonable interpretation and as such, a small inhibitory RNA as claimed embraces any small RNA molecule capable of inhibiting expression of a DNA repair protein.

Collis et al. teach a method of treating human prostate cancer cells LNCaP with a ribozyme molecule targeted to a gene encoding a RAD51 protein wherein the cells were then irradiated with a ^{60}Co-gamma ray source (Gy) DNA damaging agent (see page 1536 last paragraph). Collis et al. teach RAD51 is a key DNA repair protein that works in the homologous repair (HRR) pathway and a decrease in this protein increases radiosensitivity of cancer cells (see page 1534). Collis et al. teach the ribozyme comprises two single stranded oligonucleotides targeted to base pairs of the RAD51 mRNA (see page 1535) and teach the combination of the ribozyme and the Gy radiation killed the LNCaP cells (see Figure 4).

Thus Collis et al. anticipates claim 1 of the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fan et al. (Cancer Gene Therapy 2000, Vol. 7, No. 10: 1307-1314), Hammond et al. and Tuschl et al (WO 02/44321).

The instant claims are drawn to a method of killing a tumor cell comprising contacting the cell with at least one small inhibitory RNA (siRNA) specific for a DNA repair protein and at least one DNA damaging agent, wherein the DNA repair protein is ATM and wherein the siRNA is encoded by a nucleic acid sequence having SEQ ID No. 4.

Fan et al. teach a method of killing human prostate cells comprising contacting the cells with an antisense construct targeted to the Ataxia telangiectasia mutated (ATM) DNA repair protein (see page 1309 column 1 and Genbank U33841 cited on PTO form 892). Fan et al. teach the antisense was generated from a human ATM cDNA translational start domain (nucleobases 188 to 445) (see page 1308, column 1). The cDNA of the human ATM DNA repair gene is not disclosed by the instant specification but is referenced by Fan et al. and can be found in Genbank as Accession No. U33841. Fan teach the transcriptional start domain of the human ATM gene is nucleotides 188 to 445 and regions 395 to 445 are encompassed in the instantly claimed SEQ ID No. 4 (see Figure 15, Oligo-A). Fan et al. teach ATM antisense from the transcriptional start domain are capable of down regulating expression of the ATM DNA repair protein when administered to human prostate cancer cells (see page 1310) and further Fan et al. teach human prostate cells transfected with ATM antisense

construct and subsequently exposed to raditon had decreased growth (see page 1310). Fan et al. does not teach a siRNA targeted to a DNA repair gene.

Hammond et al. teach two methods for silencing specific genes: antisense and RNA interference. Hammond et al. teach that although antisense methods are straightforward techniques for probing gene function, the methods have suffered from "...questionable specificity and incomplete efficacy." (see page 110, column 1). Hammond et al. further teach " "...dsRNAs have been shown to inhibit gene expression in a sequence-specific manner" and further "RNAi is a potent method, requiring only a few molecules of dsRNA per cell to silence expression."

Tuschl et al. teach siRNA molecules and teach compositions comprising siRNA and an acceptable carrier that are capable of silencing gene expression (see page 9, lines 17-25). Tuschl et al. teach that siRNAs represent a new alternative to antisense or ribozyme therapeutics.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a siRNA molecule, as taught by Hammond et al. and Tuschl et al. to target a gene encoding a DNA repair protein, as taught by Fan et al.

One would have been motivated to use a siRNA to inhibit expression of DNA repair protein such as ATM because Fan et al. teach the ATM gene is a key mediator of damaged DNA repair and cellular recovery and teach reduced expression of ATM aids in decreased survival of irradiated cancer cells. Fan et al. explains that irradiated cancer cells with normal levels of DNA repair proteins such as ATM proceed thru the normal cell cycle and continue with DNA replication which often leads to further

enhanced chromosomal aberrations and reduced cell survival (see page 1313, column 1) therefore one would have been motivated to use a siRNA targeted to ATM to reduce expression of said DNA repair protein. One would have been further motivated to generate a siRNA from the claimed sequence given Fan et al. teach antisense from the translational start region were capable of significantly reducing the expression from human prostate cancer cells after treatment with a construct expressing ATM antisense (see age 1310). One of skill in the art would have been motivated to use a siRNA targeted to a ATM gene instead of an antisense because it was well known at the time the invention was made that siRNA molecules are efficient molecules to target and decrease expression of a target gene and because Hammond et al. teach using siRNA to inhibit gene expression is more sequence specific than using antisense methodologies and RNAi using dsRNA is a more potent method requiring only a few molecules of dsRNA per cell.

One would have a reasonable expectation of success given that Tuschl et al. teach how to make and use virtually any siRNA to any gene provided the target sequence is known and teach that methods of RNA synthesis are known in the art, as evidenced by the examples provided therein. Further, one would have expected success at generating a siRNA targeted at the translational start region of the ATM that is capable of inhibiting gene expression given Fan et al. teach an inhibitory molecule generating from the same region that was capable of decreasing ATM DNA repair protein expression.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Kimberly Chong/
Examiner
Art Unit 1635